Storage Mechanisms and Control in Carbohydrate Metabolism 1

SUMMARY

Section 18.1

- Glycogen is the storage form of glucose in animals, including humans. Glycogen releases glucose when energy demands are high.
- Glucose polymerizes to form glycogen when the organism has no immediate need for the energy derived from glucose breakdown.
- Glycogen metabolism is subject to several different control mechanisms, including covalent modification and allosteric effects

Section 18.2

- Glucose is formed from pyruvate, which, in turn, can be obtained from lactate that accumulates in muscle during exercise. This process, called gluconeogenesis, takes place in the liver after lactate is transported there by the blood. The newly formed glucose is transported back to the muscles by the blood.
- Gluconeogenesis bypasses the irreversible reactions of glycolysis. Oxaloacetate is an intermediate in this pathway.

Section 18.3

- A number of control mechanisms operate in carbohydrate metabolism. They include allosteric effects, covalent modification, substrate cycles, and genetic control. These mechanisms affect key enzymes in different ways with different time responses.
- In the mechanism of substrate cycling, the synthesis and the breakdown of a given compound are catalyzed by two different enzymes. Energy is required, but independent control can be exercised over the two opposing processes to avoid a futile cycle that wastes energy.

Section 18.4

- In the pentose phosphate pathway, two important processes take place. One is the formation of five-carbon sugars, particularly ribose, a component of RNA.
- The other is the formation of NADPH, a reducing agent required in many anabolic reactions

LECTURE NOTES

The material in this chapter extends carbohydrate metabolism beyond glycolysis. Glycogen metabolism and gluconeogenesis add relatively few new reactions and enzymes to students' repertoires, and regulatory control mechanisms can be the primary focus of discussion. The reactions of the pentose phosphate pathway may be discussed in depth or the focus may also primarily be on regulation. This chapter should require no more than two lectures.

LECTURE OUTLINE

I. Glycogen metabolism
    A. Glycogen breakdown
        1. Glycogen phosphorylase
        2. Phosphoglucomutase
        3. Debranching enzyme
    B. Formation of glycogen
        1. Use of UTP
        2. Glycogen synthase
        3. Branching enzyme
    C. Control mechanisms
        1. Covalent modification of phosphorylase
        2. Hormonally regulated enzyme cascade
        3. Allosteric control of phosphorylase
        4. Allosteric control of glycogen synthase
        5. Reciprocal control via enzyme cascade

II. Gluconeogenesis
    A. Importance of oxaloacetate
        1. Pyruvate carboxylase
        2. Biotin
        3. PEPCK
        4. Thermodynamic considerations
    B. Role of sugar phosphates
        1. Fructose-1,6-bisphosphatase
        2. Glucose-6-phosphatase

III. Control of carbohydrate metabolism
    A. Control of PFK and FBPase
        1. Fructose-2,6-bisphosphate
        2. Regulation of PFK-2/FBPase-2 of phosphorylation
        3. Substrate cycling
        4. Cori cycle
    B. Control of pyruvate kinase
    C. Control of hexokinase
    D. Cori cycle

IV. The pentose phosphate pathway
    A. Oxidative reactions
        1. Glucose-6-phosphate dehydrogenase
        2. 6-phosphogluconate dehydrogenase
    B. Nonoxidative reactions
        1. Epimerase
        2. Isomerase
        3. Transketolase
        4. Transaldolase
    C. Control

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ANSWERS TO EXERCISES

18.1 How Glycogen Is Produced and Degraded

1. These two pathways occur in the same cellular compartment, and, if both are on at the same time, a futile ATP hydrolysis cycle results. Using the same mechanism to turn them on/off or off/on is highly efficient.
2. In phosphorolysis, a bond is cleaved by adding the elements of phosphoric acid across that bond, whereas in hydrolysis, the cleavage takes place by adding the elements of water across the bond.
3. Glucose-6-phosphate is already phosphorylated. This saves one ATP equivalent in the early stages of glycolysis.
4. Each glucose residue is added to the growing glycogen molecule by transfer from UDPG.
5. Glycogen synthase is subject to covalent modification and to allosteric control. The enzyme is active in its phosphorylated form and inactive when dephosphorylated. AMP is an allosteric inhibitor of glycogen synthase, whereas ATP and glucose-6- phosphate are allosteric activators.
6. There is a net gain of three, rather than two, ATP when glycogen, not glucose, is the starting material of glycolysis.
7. It “costs” one ATP equivalent (UTP to UDP) to add a glucose residue to glycogen. In degradation, about 90% of the glucose residues do not require ATP to produce glucose-1-phosphate. The other 10% require ATP to phosphorylate glucose. On average, this is another 0.1 ATP. Thus, the overall “cost” is 1.1 ATP, compared with the three ATP that can be derived from glucose-6-phosphate by glycolysis.
8. The ATP cost is the same, but more than 30 ATP can be derived from aerobic metabolism.
9. Eating high-carbohydrate foods for several days before strenuous activity is intended to build up glycogen stores in the body. Glycogen will be available to supply required energy.
10. The disaccharide sucrose can be hydrolyzed to glucose and fructose, which can both be readily converted to glucose-1-phosphate, the immediate precursor of glycogen. This is not the usual form of “glycogen loading.”
11. Probably not, because the sugar spike initially results in a rapid increase in insulin levels, which results in lowering blood glucose levels and increased glycogen storage in the liver.
12. The sprint is essentially anaerobic and produces lactate from glucose by glycolysis. Lactate is then recycled to glucose by gluconeogenesis.
13. It is unlikely that this finding will be confirmed by other researchers. The highly branched structure of glycogen is optimized for release of glucose on demand.
14. Each glucose residue added to a growing phosphate chain comes from uridine diphosphate glucose. The cleavage of the phosphate ester bond to the nucleoside diphosphate moiety supplies the needed energy.

15. The enzyme that catalyzes addition of glucose residues to a growing glycogen chain cannot form a bond between isolated glucose residues; thus we have the need for a primer.
16. The glycogen synthase reaction is exergonic overall because it is coupled to phosphate ester hydrolysis.
17.

(a) Increasing the level of ATP favors both gluconeogenesis and glycogen synthesis.
(b) Decreasing the level of fructose-1,6-*bis*phosphate would tend to stimulate glycolysis, rather than gluconeogenesis or glycogen synthesis.
(c) Levels of fructose-6- phosphate do not have a marked regulatory effect on these pathways of carbohydrate metabolism.

18. “Going for the burn” in a workout refers to the sensation that accompanies lactic acid buildup. This in turn arises from anaerobic metabolism of glucose in muscle.
19. Sugar nucleotides are diphosphates. The net result is hydrolysis to two phosphate ions, releasing more energy and driving the addition of glucose residues to glycogen in the direction of polymerization.

18.2 Gluconeogenesis Produces Glucose from Pyruvate

20. Reactions that require acetyl-CoA: none. Reactions that require biotin: carboxylation of pyruvate to oxaloacetate.
21. Three reactions of glycolysis are irreversible under physiological conditions. They are the production of pyruvate and ATP from phosphoenolpyruvate, the production of fructose-1,6-*bis*phosphate from fructose-6-phosphate, and the production of glucose-6- phosphate from glucose. These reactions are bypassed in gluconeogenesis; the reactions of gluconeogenesis differ from those of glycolysis at these points and are catalyzed by different enzymes.
22. Biotin is the molecule to which carbon dioxide is attached to the process of being transferred to pyruvate. The reaction produces oxaloacetate, which then undergoes further reactions of gluconeogenesis.
23. In gluconeogenesis, glucose-6-phosphate is dephosphorylated to glucose (the last step of the pathway); in glycolysis, it isomerizes to fructose-6-phosphate (an early step in the pathway).
24. Of the three processes—glycogen formation, gluconeogenesis, and the pentose phosphate pathway—only one, gluconeogenesis, involves an enzyme that requires biotin. The enzyme in question is pyruvate carboxylase, which catalyzes the conversion of pyruvate to oxaloacetate, an early step in gluconeogenesis.
25. The hydrolysis of fructose-1,6-*bis*phosphate is a strongly exergonic reaction. The reverse reaction in glycolysis, phosphorylation of fructose-6-phosphate, is irreversible because of the energy supplied by ATP hydrolysis.

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18.3 Control of Carbohydrate Metabolism

26. Reactions that require ATP: formation of UDP-glucose from glucose-1-phosphate and UTP (indirect requirement, because ATP is needed to regenerate UTP), regeneration of UTP, and carboxylation of pyruvate to oxaloacetate. Reactions that produce ATP: none. Enzymes that catalyze ATP-requiring reactions: UDP-glucose phosphorylase (indirect requirement), nucleoside phosphate kinase, and pyruvate carboxylase. Enzymes that catalyze ATP-producing reactions: none.
27. Fructose-2,6-*bis*phosphate is an allosteric activator of phosphofructokinase (a glycolytic enzyme) and an allosteric inhibitor of fructose *bis*phosphate phosphatase (an enzyme in the pathway of gluconeogenesis).
28. Hexokinase can add a phosphate group to any of several six-carbon sugars, whereas glucokinase is specific for glucose. Glucokinase has a lower affinity for glucose than does hexokinase. Consequently, glucokinase tends to deal with an excess of glucose, particularly in the liver. Hexokinase is the usual enzyme for phosphorylating six-carbon sugars.
29. The Cori cycle is a pathway in which there is cycling of glucose due to glycolysis in muscle and gluconeogenesis in liver. The blood transports lactate from muscle to liver and glucose from liver to muscle.
30. Substrate cycles are futile in the sense that there is no net change except for the hydrolysis of ATP. However, substrate cycles allow for increased control over opposing reactions when they are catalyzed by different enzymes.
31. Having two control mechanisms allows for fine-tuning of control and for the possibility of amplification. Both mechanisms are capable of rapid response to conditions, milliseconds in the case of allosteric control and seconds to minutes in the case of covalent modification.
32. Different control mechanisms have inherently different time scales. Allosteric control can take place in milliseconds, whereas covalent control takes seconds to minutes. Genetic control has a longer time scale than either.
33. The most important aspect of the amplification scheme is that the control mechanisms affect agents that are catalysts themselves. An enhancement by several powers of ten is itself increased by several powers of ten.
34. Enzymes, like all catalysts, speed up the forward and reverse reaction to the same extent. Having different catalysts is the only way to ensure independent control over the rates of the forward and reverse process.
35. Muscle tissue uses large quantities of glucose, producing lactate in the process. The liver is an important site of gluconeogenesis to recycle the lactate to glucose.
36. Fructose-2,6-*bis*phosphate is an allosteric activator of phosphofructokinase (a glycolytic enzyme) and an allosteric inhibitor of fructose *bis*phosphate phosphatase (an enzyme in the pathway of gluconeogenesis). It thus plays a role in two pathways that are not exactly the reverse of each other.
37. The concentration of fructose-2,6-*bis*phosphate in a cell depends on the balance between its synthesis (catalyzed by phosphofructokinase-2) and its breakdown (catalyzed by fructose *bis*phosphatase-2). The separate enzymes that control the formation and breakdown of fructose-2,6-*bis*phosphate are themselves controlled by a phosphorylation/dephosphorylation mechanism.

38. Glycogen is more extensively branched than starch. It is a more useful storage form of glucose for animals because the glucose can be mobilized more easily when there is a need for energy.
39. In the glucose-6-phosphatase reaction, the concentration of substrate is the main determinant of reaction velocity. In the fructose-1,6-*bis*phosphatase reaction, allosteric effects are the main determinant of reaction velocity.
40. AMP and fructose-2,6-*bis*phosphate are allosteric activators of phosphofructokinase. The are allosteric inhibitors of fructose-1,6-*bis*phosphatase.
41. Allosteric effects and covalent modification are two important forms of control of enzymatic action. Covalent modification plays a more important role that allosteric effects in glycogen breakdown.
42. Insulin triggers the series of events that leads to glycogen synthesis.
43. Glucagon and epinephrine start the chain of events leading to glucagon breakdown.
44. Glucagon is a peptide, whereas epinephrine is an amino acid derivative.

18.4 Glucose Is Sometimes Diverted through the Pentose Phosphate Pathway

45. NADPH has one more phosphate group than NADH (at the 2′ position of the ribose ring of the adenine nucleotide portion of the molecule). NADH is produced in oxidative reactions that give rise to ATP. NADPH is a reducing agent in biosynthesis. The enzymes that use NADH as a coenzyme are different from those that require NADPH.
46. Glucose-6-phosphate can be converted to glucose (gluconeogenesis), glycogen, pentose phosphates (pentose phosphate pathway), or pyruvate (glycolysis).
47. Hemolytic anemia is caused by defective working of the pentose phosphate pathway. There is a deficiency of NADPH, which indirectly contributes to the integrity of the red blood cells. The pentose phosphate pathway is the only source of NADPH in red blood cells.
48.

(a) By using only the oxidative reactions.
(b) By using the oxidative reactions, the transaldolase and transketolase reactions, and gluconeogenesis.
(c) By using glycolytic reactions and the transaldolase and transketolase reactions in reverse.

49. Transketolase catalyzes the transfer of a two-carbon unit, whereas transaldolase catalyzes the transfer of a three-carbon unit.
50. In red blood cells, the presence of the reduced form of glutathione is necessary for the maintenance of the sulfhydryl groups of hemoglobin and other proteins in their reduced forms, as well as for keeping the Fe(II) of hemoglobin in its reduced form. Glutathione also maintains the integrity of red cells by reacting with peroxides that would otherwise degrade fatty-acid side chains in the cell membrane.
51. Thiamine pyrophosphate is a cofactor necessary for the function of transketolase, an enzyme that catalyzes one of the reactions in the nonoxidative part of the pentose phosphate pathway.

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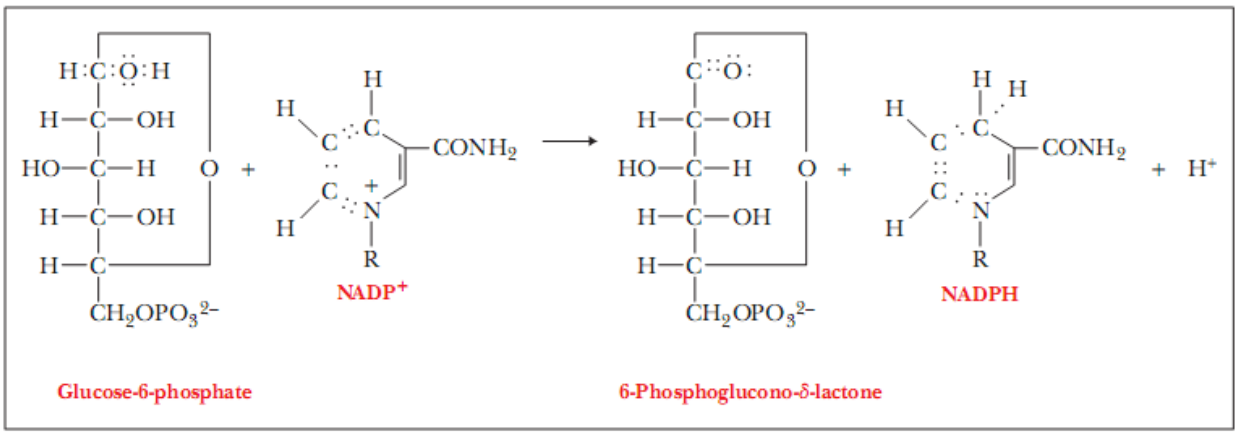
52.



53. Having different reducing agents for anabolic and catabolic pathways keeps the pathways separate metabolically. Thus, they are subject to independent control and do not waste energy.

54. If a cell needs NADPH, all the reactions of the pentose phosphate pathway take place. If a cell needs ribose-5-phosphate, the oxidative portion of the pathway can be bypassed; only the nonoxidative reshuffling reactions take place. The pentose phosphate pathway does not have a significant effect on the cell's supply of ATP.

55. The ester bond is more easily broken than any of the other bonds that form the sugar ring. Hydrolysis of that bond is the next step in the pathway.

56. The reshuffling reactions of the pentose phosphate pathway have both an epimerase and an isomerase. Without an isomerase, all the sugars involved are keto sugars, which are not substrates for transaldolase, one of the key enzymes in the reshuffling process.